Multimodality Treatment for Cerebral Arteriovenous Malformations
—Complementary Role of Proton Beam Radiotherapy—

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Abstract

A total of 29 cerebral arteriovenous malformations (AVMs) treated at the University of Tsukuba with multimodality treatment including proton beam (PB) radiotherapy for cerebral AVMs between 2005 and 2011 were retrospectively evaluated. Eleven AVMs were classified as Spetzler-Martin grades I and II, 10 as grade III, and 8 as grades IV and V. For AVMs smaller than 2.5 cm and located on superficial and non-eloquent areas, surgical removal with/without embolization was offered as a first-line treatment. For some small AVMs located in deep or eloquent lesions, gamma knife (GK) radiosurgery was offered. Some AVMs were treated with only embolization. AVMs larger than 2.5 cm were embolized to achieve reduction in size, to enhance the safety of the surgery, and to render the AVM amenable to GK radiosurgery. For larger AVMs located in deep or eloquent areas, PB radiotherapy was offered with/without embolization. Immediately after the treatment, 24 patients exhibited no neurological worsening. Four patients had moderate disability, and 1 patient had severe disability. Three patients suffered brain damage after surgical resection, and 2 patients suffered embolization complications. However, no neurological worsening was observed after either GK radiosurgery or PB radiotherapy, but 3 patients treated by PB radiotherapy suffered delayed hemorrhage. Fractionated PB radiotherapy for cerebral AVMs seems to be useful for the treatment of large AVMs, but careful long-term follow up is required to establish the efficacy and safety.

Key words: arteriovenous malformation, embolization, microsurgery, multimodality treatment, proton beam radiotherapy

Introduction

The complex cerebrovascular anatomy of arteriovenous malformations (AVMs) creates challenging problems, and the various treatments are associated with significant risks. Microsurgery, stereotactic radiosurgery (SRS), and endovascular embolization have all been used to treat AVMs as either single or combined methods. However, these various therapies have limited utility in the treatment of large AVMs. Gamma knife (GK) radiosurgery has limited utility because of the adjusted prescription dose-volume relationship, which leads to substantially
lower cure rates and higher complication rates for large AVMs (> 3 cm in diameter). Endovascular embolization has limited utility because of the overall limitations as a curative procedure for large and small AVMs. Therefore, large AVMs generally require staged, and often combination, approaches.\(^3,26\)

Charged particle beams used under stereotactic conditions offer the possibility of treatment for large AVMs with low complication rate.\(^1,4,8,10,21,24\) The pattern of energy distribution of the proton beam (PB) is characterized by the entrance region with slowly rising dose, rapid rise to the maximum dose (the Bragg peak), and subsequent fall to nearly zero. Irradiation of larger targets is achieved by superimposing PBs of different energies, thereby generating a dose distribution that provides a moderate entrance dose, a uniform high dose within the target tissue, and a zero dose beyond the target. Since 1990, we have used PB radiotherapy for patients with AVMs at the Proton Medical Research Center of the University of Tsukuba.\(^10\)

Here, we describe the strategy and immediate results of multimodality treatment including PB radiotherapy for cerebral AVMs.

### Materials and Methods

A total of 29 patients with cerebral AVMs, 18 females and 11 males aged 5 to 61 years (mean 30.2 years), were treated at the University of Tsukuba between April 2005 and December 2011. The presenting symptoms included hemorrhages (14 patients), headaches (7), neurological declines due to vascular steal phenomenon (2), seizure (1), mass effect of a flow-related aneurism (1), and incidental finding (4). All AVMs were diagnosed on the basis of magnetic resonance (MR) imaging and cerebral angiography, and the nidus size was defined as the maximum diameter on MR imaging. The mean nidus size was 34 mm (range 10–70 mm). The AVMs were classified using the Spetzler-Martin grading system (size of the AVM, eloquence of the adjacent brain, and presence/absence of deep venous drainage).\(^22,23\) Eleven AVMs were classified as Spetzler-Martin grades I and II, 10 as grade III, and 8 as grades IV and V.

The AVM treatment strategy was based on the MR images and cerebral angiograms in a joint meeting of neurosurgeons and neuroradiologists. In general, for AVMs smaller than 2.5 cm and located on superficial and non-eloquent area, surgical removal with/without embolization was offered as a first-line treatment with complete cure of the AVMs. For some small AVMs located in deep or eloquent areas, GK radiosurgery was offered. AVMs larger than 2.5 cm were embolized to achieve reduction in size, to enhance the safety of the surgery, and to render the AVM amenable to GK radiosurgery. For larger AVMs located in deep or eloquent areas, PB radiotherapy was offered with/without embolization (Fig. 1).

### Results

Surgical resection without embolization was performed in 3 patients. Endovascular embolization was performed in 19 patients in 29 sessions (mean 1.5 sessions per patient). Three patients underwent only endovascular embolization, 10 patients underwent pre-surgical embolization, and 6 patients underwent pre-radiosurgical embolization (GK radio-

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**Fig. 1** Schema of the treatment protocol for cerebral arteriovenous malformations (AVMs). GK: gamma knife, PB: proton beam.
Table 1  Patients treated by proton beam (PB) radiotherapy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>AVM location</th>
<th>Size (mm)</th>
<th>Spetzler-Martin grade</th>
<th>Symptom</th>
<th>Treatment</th>
<th>PB dose (GyE/fx)</th>
<th>Early complication</th>
<th>Delayed hemorrhage</th>
<th>Follow up findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23/F</td>
<td>lt occipital</td>
<td>36</td>
<td>III</td>
<td>headache</td>
<td>PB + Ope</td>
<td>36.9/6</td>
<td>-</td>
<td>+ (40 mos)</td>
<td>alive, complete removal (44 mos)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>71/M</td>
<td>lt temporal</td>
<td>30</td>
<td>III</td>
<td>vertigo</td>
<td>Embo + PB</td>
<td>45/15</td>
<td>-</td>
<td>-</td>
<td>alive (37 mos)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>47/F</td>
<td>lt occipital</td>
<td>30</td>
<td>III</td>
<td>incidental</td>
<td>PB</td>
<td>36/6</td>
<td>-</td>
<td>-</td>
<td>alive (37 mos)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20/M</td>
<td>lt parieto-occipital</td>
<td>57</td>
<td>III</td>
<td>headache</td>
<td>Embo + PB</td>
<td>24/4</td>
<td>-</td>
<td>-</td>
<td>alive (42 mos)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21/M</td>
<td>lt occipital</td>
<td>56</td>
<td>IV</td>
<td>incidental</td>
<td>Embo + PB</td>
<td>46.2/11</td>
<td>-</td>
<td>-</td>
<td>alive, complete obliteration (84 mos)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>40/M</td>
<td>rt frontal</td>
<td>56</td>
<td>IV</td>
<td>headache</td>
<td>PB</td>
<td>36/6</td>
<td>-</td>
<td>+ (21 mos)</td>
<td>dead (21 mos)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>27/F</td>
<td>lt frontal</td>
<td>60</td>
<td>IV</td>
<td>vascular steal</td>
<td>PB</td>
<td>39.6/6</td>
<td>-</td>
<td>+ (16 mos)</td>
<td>alive (31 mos)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>58/F</td>
<td>rt fronto-parietal</td>
<td>70</td>
<td>V</td>
<td>vascular steal</td>
<td>PB</td>
<td>36/6</td>
<td>-</td>
<td>-</td>
<td>alive (18 mos)</td>
<td></td>
</tr>
</tbody>
</table>


surgery or PB radiotherapy). Five patients received only GK radiosurgery or PB radiotherapy. The clinical features of the AVMs treated by PB radiotherapy are summarized in Table 1. Multimodality combination therapy was performed in 2 patients. One patient underwent surgical resection after embolization and GK radiosurgery. One patient underwent surgical resection after PB radiotherapy (Fig. 2).

Immediately after the treatment, 24 patients exhibited no neurological worsening. Four patients had moderate disability, and 1 patient had severe disability. Three patients suffered brain damage after surgical resection of Spetzler-Martin grade II, grade III, and grade IV AVMs in one patient each. One patient with Spetzler-Martin grade IV AVM suffered intracerebral hemorrhage after endovascular embolization. One patient with Spetzler-Martin grade II AVM suffered minor infarction after endovascular embolization. No neurological worsening was observed in patients who underwent GK radiosurgery or PB radiotherapy.

Complete AVM removal was achieved in 13 patients who underwent surgical resection with/without embolization. Three patients underwent only endovascular treatment, and complete obliteration was achieved. Complete AVM obliteration was achieved in 1 patient who underwent PB radiotherapy with embolization. The remaining 12 patients who underwent either GK radiosurgery or PB radiotherapy were included in the follow-up evaluation. Three patients treated by PB radiotherapy suffered delayed hemorrhage during the follow-up period (mean 39.2 months). One of the 3 patients died, 1 was treated conservatively, and 1 was treated surgically in the chronic phase.

Illustrative Case

A 21-year-old man presented with a left occipital large AVM (Spetzler-Martin grade IV) detected incidentally (Fig. 3A–C). He was initially treated with pre-radiosurgical embolization, followed by fractionated PB radiotherapy (46.2 Gy-equivalents/11 fractions). Follow-up MR angiography obtained 81 months after the PB radiotherapy revealed marked decrease in size of the AVM nidus (Fig. 3D). Cerebral angiography obtained 84 months after the treatment revealed complete obliteration of the AVM (Fig. 3E, F). His neurological status remained intact during the follow-up period.

Discussion

Cerebral AVMs carry significant risks of morbidity and mortality related to intracerebral hemorrhages, seizures, and progressive ischemic neurological decline caused by either vascular steal phenomenon or venous hypertension. In a long-term follow-up study, AVMs with previous rupture and large size, as well as AVMs in infratentorial and deep locations, had the highest risk of subsequent hemorrhage. The morbidity and mortality rates associated with the complete obliteration of Spetzler-Martin grade I and II AVMs accomplished with only microsurgery and with only SRS have been minimal. However, these treatment options are far less appealing for more complex grade IV and V AVMs, because of the significantly higher morbidity and mortality rates.

The American Heart Association does not recommend surgery for large AVMs, AVMs involving deep veins, or AVMs in Spetzler-Martin grade IV or V.

Endovascular embolization is often used to reduce
Fig. 2 Profile of the multimodality treatment for cerebral arteriovenous malformations of Spetzler-Martin grades I and II (A), grade III (B), and grades IV and V (C). GK: gamma knife, PB: proton beam.

Fig. 3 Illustrative case. A: Axial T2-weighted magnetic resonance (MR) image showing a left occipital large arteriovenous malformation (AVM). B: Left carotid angiogram revealing a large occipital AVM (Spetzler-Martin grade IV). C: Left vertebral angiogram showing a large occipital AVM. D: Follow-up axial T2-weighted MR image obtained 81 months after the proton beam radiotherapy revealing marked decrease in size of the AVM nidus. E: Left carotid angiogram obtained 84 months after the treatment revealing complete obliteration of the AVM. F: Left vertebral angiogram revealing complete obliteration of the AVM.

the blood flow, particularly that of any deep feeders, to reduce the risks associated with surgical resection or to reduce the size of the lesion for radiosurgery.2,3,6,14,25,26) Endovascular embolization was formerly used as a palliative treatment. The complete cure rate obtained in a series of N-butyl-2-cyanoacrylate embolizations varied by around 10%. In recent years, the introduction of Onyx, a nonadhesive agent with longer polymerization time, has led to better penetration of the nidus with slower filling. The results of AVM nidus embolization have shown significant improvement with the introduction of Onyx.11,14,25) Complete obliteration with only Onyx embolization was achieved in 98% of Spetzler-Martin grade I and II AVMs, but in only 12.5% of Spetzler-Martin grade III–V AVMs.18) The risk of hemorrhage from AVMs after partial embolization was 3.95% per year, compared with 4.79% per year for AVMs without embolization, revealing no evidence that partial embolization reduced future hemorrhage risks from the AVMs.5) In our strategy, some patients with AVMs that have hemorrhaged may also benefit from target embolization for the specific component of the likely site of hemorrhage (e.g., an associated aneurysm), and were mainly included in the pre-radiosurgical embolization group.13)

SRS has become an important modality for the...
treatment of AVMs. Retrospective analysis of 400 patients with small AVMs who were treated with GK radiosurgery revealed complete obliteration rates of 72% at 3 years and 87.3% at 5 years.\(^{10}\) In contrast, GK radiosurgery for large AVMs generally has poor results. The overall obliteration rate following repeated GK radiosurgeries was 34.1%, and the estimated obliteration rate at 120 months was 41.8%.\(^{12}\) Volume-staged GK radiosurgery is a modern approach used to treat large AVMs. However, the complete obliteration rate of 50% with post-radiosurgical hemorrhages occurring in 14% of the cases is not encouraging.\(^{20}\) Increasing treatment volumes and radiation doses are clearly associated with increases in complications. In patients with treatment volume >30 cm\(^3\), post-radiosurgical imaging changes developed within the peripheral neural regions in 78% of patients, and symptomatic complications developed in 50%.\(^{10}\)

Protons are generated by stripping a hydrogen atom of its electron and accelerating the residual proton in the magnetic field of a synchrotron. The pattern of energy distribution of the PB is characterized by the entrance region slowly rising dose, rapid rise to the maximum dose (Bragg peak), and fall to nearly zero.\(^{4}\) These unique physical characteristics of PBs offer considerable advantages in the treatment of large AVMs.\(^{1,4,8,10,21,25}\) Our previously reported long-term outcome of PB radiotherapy for large AVMs achieved complete obliteration in 9 of 11 patients. All patients underwent pre-radiosurgical embolization, which was aggressively performed in vessels if considered safe. None of the patients experienced complete obliteration following the embolization. The mean time from treatment to complete obliteration was 58.8 months. One patient suffered post-radiosurgical hemorrhage at 138 months after PB radiotherapy, and one patient suffered radiation necrosis in the follow-up period.\(^{10}\)

Recently, we introduced fractionated PB radiotherapy for large cerebral AVMs. Although the increased total radiation dose using fractionation and multi-staged treatments may be a safe method for reducing radiation-related complications, the trade-off seems to be a lower obliteration rate. Endovascular embolization using Onyx followed by either GK or PB radiotherapy may be a useful approach to effectively reduce the target volume, thus increasing the obliteration rates and reducing radiation-related complications.\(^{15}\) Targeted embolizations at the site of the hemorrhage or preventive embolizations for pedicle aneurysms followed by PB radiotherapy may also be another approach for hemorrhaged or non-hemorrhaged large AVMs. However, delayed hemorrhage from AVMs occurred in 3 patients treated by PB radiotherapy, so any decision about the validity for PB radiotherapy would be premature. This series was very small and the mean follow-up was only 39.2 months. However, we suggest that multimodality treatment combined with PB radiotherapy is a useful option for large and deeply located cerebral AVMs.

References

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